Int. J. Cancer: **88,** 139–145 (2000)
Published 2000 Wiley-Liss, Inc.

Publication of the International Union Against Cancer

LUNG CANCER AND ENVIRONMENTAL TOBACCO SMOKE IN A NON-INDUSTRIAL AREA OF CHINA

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We report results from a population-based case-control study of lung cancer and environmental tobacco smoke (ETS) among never-smokers conducted in 2 rural prefectures of China, including 200 female and 33 male lung cancer cases, and 407 female and 114 male controls, matched on age, sex and prefecture of current residence. The odds ratio (OR) for ever-exposed to ETS was 1.19 (95% CI 0.7–2.0), with a significant trend (*p*<0.05) with increasing exposure. ORs were 1.00, 1.04, 1.13 and 1.51 for non-exposed, <10, 10–19 and ≥20 pack-years of ETS exposure, respectively. Excess risks were limited to ETS exposures in childhood (≤18 years of age). The OR for ever-exposed to ETS in childhood, adjusting for ETS exposure in adulthood, was 1.52 (95% CI 1.1–2.2), with a significant trend (*p*<0.01) with increasing pack-years of childhood exposure, 1.00, 1.43, 1.81 and 2.95, respectively. After adjustment for ETS in childhood, there was no excess risk from adult ETS exposure. The OR for ever-exposed to ETS in adulthood was 0.90 (95% CI 0.–1.4). These results were not affected by adjustment for type of residential dwelling, type or amount of fuel used, perceived indoor smokiness, or measures of socioeconomic status, or omitting next-of-kin respondents. *Int. J. Cancer* 88:139–145, 2000.
Published 2000 Wiley-Liss, Inc.†

Epidemiologic studies of lung cancer and exposure to environmental tobacco smoke (ETS) have been conducted in countries throughout the world and consistently show a 1.2- to 1.5-fold risk of lung cancer (National Research Council, 1986; California Environmental Protection Agency, 1997). Studies of ETS exposure in China however are of particular interest, due to the high lung cancer rate in females who are mostly non-smokers (Gao *et al*., 1987; Xu *et al*., 1989; Wu-Williams *et al*., 1990; Blot and Fraumeni, 1996) and due to the relatively low odds ratios (OR) of lung cancer among active smokers, where ORs for ever-smokers compared with never-smokers consistently range from 2 to 4 (Liu, 1992; Liu *et al*., 1998), markedly lower than in western countries (U. S. Department of Health and Human Services, 1990). The rates of lung cancer for females in China are high, although not uniformly so across the country, and may be due to indoor air pollutants, diet, cooking oil fumes, occupational factors and non-malignant respiratory diseases, as well as ETS (Blot and Fraumeni, 1996), while the lower overall ORs for active smoking among Chinese adults may be attributable to later age at smoking initiation (Yang *et al*., 1999), relatively shorter duration of smoking, less intense inhalation practices or the greater proportion of pipe, as compared with cigarette, smokers (Liu, 1992; Lubin *et al*., 1992). Nonetheless, ORs of 20-fold have been reported in those smoking 20 cigarettes per day or more (Xu *et al*., 1989), suggesting that Chinese smokers are not at an inherently lower risk of lung cancer.

Results from studies of residential ETS exposure in China have been mixed (Chan and Fung, 1982; Lam, 1985, 1987; Gao *et al*., 1987; Koo *et al*., 1987; Geng *et al*., 1988; Wu-Williams *et al*., 1990; Liu *et al*., 1991; 1993; Wang *et al*., 1994; 1996; Du *et al*., 1996; Ko *et al*., 1997; Zhong *et al*., 1999). However, several of the individual studies did not adjust for potentially important cofactors, such as indoor air pollution and occupational exposures.

Several outstanding issues concerning ETS exposure and risk of lung cancer remain. Few previous studies have evaluated factors that modify the OR for ETS exposure. Few studies have evaluated differences in risk from ETS exposure in childhood, as compared with adulthood (Gao *et al*., 1987; Janerich *et al*., 1990; Wang *et al*., 1994; Zhong *et al*., 1999). One study found a greater risk from childhood ETS exposure than from ETS exposure in adulthood (Wang *et al*., 1994), two studies found no difference in risk (Gao *et al*., 1987; Zhong *et al*., 1999) and one found an excess risk from ETS exposure only in childhood (Janerich *et al*., 1990). In addition, while there have been studies of lung cancer risk and active smoking among Chinese men, the majority of whom smoke (Gao *et al*., 1988; Qiao *et al*., 1989; Liu *et al*., 1991; Lubin *et al*., 1992; Yao *et al*., 1994; Du *et al*., 1996; Yu and Zhao, 1996; Xu *et al*., 1996; Lei *et al*., 1996; Qiao *et al*., 1997), there have been apparently no studies of ETS exposure among the few Chinese men who never smoked.

To address questions associated with lung cancer and ETS exposure, we analyzed data from a population-based case-control study of lung cancer in 2, primarily rural, prefectures in Gansu Province in north-western China. These areas are unique because more than half of the population currently live or have lived for an extended period in underground dwellings, where indoor levels of radioactive radon gas are among the highest in the world (Wang *et al*., 1996). In most residences, brick stoves are used for heating and for cooking, with smoke and fumes vented via enclosed ducts through a bed-like brick platform used for sleeping (call a *kang*) to the outside. Coal, wood, sticks or other biomass were the principal sources of fuel.

MATERIAL AND METHODS

Study subjects

Beginning in June 1995, we identified all individuals between the ages of 30 and 75 years who were newly diagnosed with lung cancer between January 1994 and April 1998, and were residents of Pingliang or Qingyang, 2 prefectures in Gansu Province, China, with a total adult population of about 4×10^6 persons. Cases were identified from 2 prefecture hospitals, a company hospital located at a nearby oilfield, 15 county hospitals and local clinics. We also reviewed records from special anti-tuberculosis reporting stations in the prefectures. In addition, hospital records in larger nearby cities, Lanzhou, Xian and Yinchuan, were reviewed for lung cancer patients diagnosed in residents of the two prefectures.

Based on clinical/radiological symptoms suggestive of lung cancer or pathological evidence, a total of 1,209 possible cases were identified. An expert panel of pathologists, radiologists and clinicians, assembled from members of the Gansu Department of

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Received 22 January 2000; Revised 20 March 2000; Accepted 20 April 2000

Health, reviewed all case diagnoses. The expert panel excluded 277 subjects due to the absence of supporting evidence or to incorrect diagnosis, leaving 932 cases. Of these, 43 cases could not be located and 3 cases moved out of the study area resulting in a total number of 886 cases (656 males and 230 females). Diagnoses of lung cancer were based on clinical/radiological criteria for 533 cases (60%) and pathological evidence (such as bronchofiberoptic biopsy, sputum cytology and lymphatic node biopsy) for 353 cases (40%).

A total of 1,966 controls was randomly selected from 1990 census lists for the 2 prefectures and frequency matched on age in 1995 to cases in 5-year age groups, within categories of sex and prefecture. The number of controls in each strata was determined by the expected age distribution for lung cancer cases obtained from a search of medical records within the prefectures for 1991 as part of a feasibility study. Twice as many controls as expected cases were selected. Among controls, 6 refused interview, 23 moved out of the study area, 62 could not be located and 35 could not be interviewed for other reasons. A total of 455 female and 1,310 male controls were included in the article.

Interviews were conducted at home or at the hospital for all cases and controls by trained interviewers using a closed-form, structured questionnaire. We asked detailed questions on demographic characteristics, smoking habits of the subject, spouse and other cohabitants, diet and cooking practices, as well as detailed occupational, residential and medical histories.

Whenever possible, interviews were conducted with the subjects themselves. If subjects were deceased or too ill, interviews were conducted with next-of-kin, usually the spouse. Next-of-kin provided information for 481 (54%) cases. Next-of-kin interviews were associated with year of lung cancer incidence. Among cases identified after 1996, 29% were next-of-kin interviews, while among cases identified in earlier calendar years, 74% were next-of-kin interviews. Next-of-kin provided information for 71 of 1,765 (4.0%) control subjects.

For the analysis of ETS exposure, we restricted data to never-smokers, defined as never smoked cigarettes or pipes regularly for 6 months or longer. There were 200 female and 33 male lung cancer cases and 407 female and 114 male controls who never smoked. Numbers for the variables in the tables differ due to missing data.

Statistical analysis

We computed odds ratios (ORs), adjusting for the reference age defined as age at disease incidence for cases and age at interview for controls, sex and prefecture, and, where appropriate, other factors using logistic regression models as implemented in the Epicure computer package (Preston *et al*., 1996). We calculated 95% Wald confidence intervals (CI) for ORs and used a score statistic for tests of trend.

ETS exposure

To estimate ETS exposure, we asked each subject or next-of-kin about the smoking habits of all cohabitants of the household during the subject's childhood, defined as ages 18 years and under, and during adulthood. The information included number of cigarettes smoked per day (store-bought), and number of *liang* (50 gm) of tobacco per month smoked as (hand-rolled) cigarettes or in Chinese long-stem pipes. The source of ETS exposure reflected the changing smoking habits in these areas of China, with pipe smoking more prevalent historically and cigarette smoking more prevalent recently. Among those exposed to ETS in childhood, 9.5, 75.2 and 15.3% were exposed from persons who smoked cigarettes only, pipes only or smoked both cigarettes and pipes, respectively. In childhood, mean ETS exposure from cigarettes was 9.6 and 10.7 cigarettes per day from cigarette only smokers and mixed smokers, respectively, while mean ETS exposure from pipes was 9.4 and 10.4 *liang* per month from pipe only and mixed smokers, respectively. The sources of ETS exposure changed in adulthood. Among those exposed to ETS in adulthood, 35.3, 27.1 and 37.6% were exposed from persons who smoked cigarettes only, pipes only or both cigarettes and pipes. Means were 14.6 and 12.5 cigarettes per day from cigarette only and mixed smokers, respectively, and 9.8 and 8.7 *liang* per month from pipe only and mixed smokers.

Initial analyses indicated that the log-linear increases in ORs for ETS exposure per cigarette smoked per day and per *liang* of tobacco smoked per month in Chinese long-stem pipes were homogeneous ($p=0.36$ and $p=0.44$ for tests of homogeneity of trends in childhood and in adulthood, respectively). ETS exposure in cigarettes per day and *liang* per month were therefore summed to obtain total ETS exposure in childhood and in adulthood. We refer to this sum as cigarettes per day of ETS exposure.

Analyses also revealed ORs for ETS exposure in childhood and in adulthood were statistically homogeneous in females and males. Consequently, unless noted, we show results for females and males combined, with adjustment for sex.

RESULTS

Table I shows the distribution of cases and controls for reference age, several demographic factors and indicators of socioeconomic level for never-smokers. By design, cases and controls for the complete data were balanced on the matching factors; however, among never-smokers, there was a smaller proportion of older female cases. This difference was primarily due to the selection of controls from the 1990 census list based on their ages in 1995. However, because the mid-point of control enrollment was 1997, the mean age at interview for controls was slightly higher than anticipated. Results also indicate that cases were more likely to have a post-primary education, have a color television or refrigerator, and own fewer large animals. While these variables were significantly related to case status, they did not confound the relationship between lung cancer and ETS-related variables. Nonetheless, in the remaining analyses, we adjusted for socioeconomic level, which was best characterized by two variables, ownership of a color television and number of cattle, as well as age, sex and prefecture.

Table II shows ORs for ever-exposed to ETS in the household, and for categories of amount of exposure, as measured by cigarette pack-years smoked by cohabitants. Overall, there was a non-significant OR of 1.19 for ever-exposed to ETS, but a significant monotonically increasing trend in ORs with pack-years of exposure (test for trend, $p=0.05$). When exposure was categorized by period of exposure, there was a statistically significant OR of 1.52 with 95% CI (1.1,2.2) for ever-exposed to ETS in childhood, and increasing ORs with pack-years of exposure ($p=0.02$). There was no effect on risk of ETS exposure occurring in adulthood. Based on a log-linear model for age, sex, prefecture, number of cattle, ownership of a color television and pack-years of exposure in childhood and in adulthood, ORs were 1.53 with 95% CI (1.1,2.1) and 1.02 with 95% CI (0.9,1.2) for each 10 pack-years of ETS exposure in childhood and in adulthood, respectively. The *p*-value for the test of homogeneity of the two trends was 0.02. The questionnaire also provided information on whether household cohabitants smoked in the presence of the subject. Adjustment for smoking in the presence of the subject did not affect the ORs in Table II.

Table II also shows that ORs were similar for males and females. None of the statistical tests of homogeneity of ORs by sex were rejected.

The two prefectures were predominantly rural with 32.8% of never-smoking males and 8.5% of never-smoking females ever employed in non-farm jobs for more than 1 year. Among never-smokers, there were 21 cases (9.0%) and 17 controls (3.3%) with some ETS exposure from non-farm jobs. After adjustment for residential ETS exposure in childhood and in adulthood and the demographic factors, the OR for any occupational ETS exposure was 1.56 with 95% CI (0.7,3.3). ORs for duration of occupational

TABLE I – DISTRIBUTION OF NEVER-SMOKING SUBJECTS AND ODDS RATIOS (OR) FOR LUNG CANCER BY CATEGORIES OF DEMOGRAPHIC VARIABLES (ORS ARE ADJUSTED FOR AGE AND PREFECTURE)

Variable	Males			Females		
	Cases (%)	Controls (%)	OR	Cases (%)	Controls (%)	OR
Reference age						
<45	24.2	17.5	1.00	19.0	12.5	1.00
45–54	18.2	33.3	0.21[1]	38.5	38.1	0.70
55–64	45.5	29.0	1.06	29.5	31.5	0.56[1]
≥65	12.1	20.2	0.45	13.0	17.9	0.51[1]
Prefecture						
1	69.7	51.8	1.00	51.0	57.0	1.00
2	30.3	48.3	0.34[1]	49.0	43.0	1.15
Education						
Primary or less	57.6	64.0	1.00	87.0	95.3	1.00
Tech/vocation	30.3	33.3	0.91	13.0	4.2	2.78[1]
College and above	12.1	2.6	6.34	0.0	0.5	—
Marital status						
Married	93.9	93.0	1.00	87.0	86.7	1.00
Widowed	6.1	6.1	1.42	12.5	13.3	1.13
Divorced	0.0	0.0	—	0.5	0.0	—
Never married	0.0	0.9	—	0.0	0.0	—
Income						
<2,000	6.1	26.3	1.00	21.5	24.4	1.00
2,000–2,999	18.2	26.3	3.25[1]	16.5	21.2	0.86
3,000–4,399	39.4	22.8	8.95[1]	28.0	28.2	1.16
≥4,000	36.4	24.6	5.61[1]	34.0	26.2	1.28
Number in household						
1–2	6.1	4.4	1.00	8.0	5.2	1.00
3–4	39.4	29.8	0.56	25.6	24.4	0.48
5–6	18.2	43.9	0.19	42.7	43.4	0.49
≥7	36.4	21.9	0.91	23.6	27.1	0.47
TV - black and white[2]	18.2	45.1	0.25[1]	51.8	49.6	1.07
TV - color[2]	51.5	20.2	3.64[1]	32.5	17.7	1.97[1]
Tape recorder[2]	50.0	33.3	1.92	31.0	29.5	1.09
Refrigerator[2]	9.1	0.9	—	7.5	2.0	3.29[1]
Number large animals						
0	54.6	33.3	1.00	54.5	32.2	1.00
1	21.2	27.2	0.58	23.0	35.4	0.44[1]
≥2	24.2	39.5	0.51	22.5	32.4	0.43[1]
Own vehicles (≥1)	12.1	9.7	1.06	10.6	5.7	1.65
Total[3]	33	114		200	407	

[1]ORs significantly differs from 1.–[2]Percentages indicate subjects with the factor.–[3]Numbers of subjects for each variable differ due to missing data.

ETS exposure of under 20 years and 20 years or more relative to no occupational exposure were 1.29 (0.5,3.3) and 1.76 (0.5,5.6), respectively, with $p=0.19$ for the test of trend with duration. When data were restricted to the 52 cases and 57 controls who ever worked in non-farm jobs, the OR for occupational ETS exposure was 1.35 with 95% CI (0.5,3.4).

We evaluated variation in the ORs with pack-years of ETS exposure in childhood and in adulthood within categories of several variables, including reference age, educational level, marital status, income and a variety of socioeconomic factors. None of the tests of homogeneity of trends in ORs across categories were rejected. We also evaluated potential confounding from factors related to indoor air pollution, by computing ORs for pack-years of ETS exposure by underground or above-ground type of current and longest lived-in dwelling, time weighted mean radon concentration in all dwellings occupied for 2 years or more 5–30 prior to the reference age, type of fuel used for heating and cooking in the current home and the subject's perceived level of indoor smokiness in winter months in the current house (Table III). Adjustment for these factors, as well as annual amount of coal used, and the degree of indoor smokiness in houses occupied as children (not shown), had little effect on ORs for pack-years of ETS exposure. Tests of homogeneity of OR trends among categories were not statistically significant, except for the trend in ORs for pack-years of ETS exposure in adulthood by type of current dwelling and type of longest lived-in dwelling. In these two cases, ORs for pack-years of ETS exposure in adulthood increased among those whose current house or longest lived-in house was an underground design. We also found no confounding of the ETS associations by prior diagnosis by a physician of one or more lung diseases, including asthma, tuberculosis, bronchitis, pneumonia, asthma or emphysema.

Finally, the results for ETS exposure were similar when data from next-of-kin interviews were omitted or only histologically confirmed cases were included. With data restricted to 115 cases and 501 controls who were self-respondents and never smoked, ORs and 95% CIs for ever exposed to ETS in childhood and adulthood were 1.75 (1.1,2.8) and 0.76 (0.4,1.3), respectively, compared with 1.52 and 0.90 for all never-smokers, and ORs increased with pack-years of ETS exposure, ORs for 0, 1–9, 10–19 and 20+ pack-years of 1.00, 1.93, 2.12 and 2.62 for childhood exposure (test for trend, $p=0.03$) and 1.00, 0.67, 0.72 and 0.63 for adulthood exposure. ORs for pack-years of ETS exposure within categories of the variables in Table III were also similar when data were restricted to self-respondents. Analyzing only histologically confirmed cases (71 or 32%), ORs and 95% CIs were 1.55 (0.9,2.8) and 0.99 (0.5,2.0), respectively.

DISCUSSION

Our study found an overall non-significant OR of 1.2 for ever-exposed to residential ETS, with a statistically significant increasing trend with pack-years of ETS exposure. The OR and 95% CI for any residential or occupational ETS exposure were 1.4

TABLE II – ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) BY EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS) IN CHILDHOOD AND ADULTHOOD FOR NEVER-SMOKING SUBJECTS [ORS FOR CHILDHOOD (ADULTHOOD) EXPOSURE ADJUSTED FOR ADULTHOOD (CHILDHOOD) EXPOSURE, REFERENCE AGE, PREFECTURE, AND SOCIOECONOMIC FACTORS. ALL ORS RELATIVE TO NO EXPOSURE TO ETS. NUMBERS VARY DUE TO MISSING DATA.]

Exposure	Males				Females				Combined[1]	
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	OR	95%CI
Lifetime ETS exposure										
No	8	42	1.00		20	43	1.00		1.00	
Yes	24	72	1.22	0.5–3.3	176	364	1.15	0.6–2.1	1.19	0.7–2.0
Pack-years[2]										
1–9	17	30	2.00	0.7–5.6	33	100	0.77	0.4–1.5	1.04	0.6–1.8
10–19	2	17	0.41	0.1–2.4	43	93	1.14	0.6–2.2	1.13	0.6–2.1
≥20	2	14	0.46	0.1–3.2	74	127	1.49[3]	0.8–2.8	1.51[3]	0.9–2.7
ETS exposure in childhood										
No	12	58	1.00		64	160	1.00		1.00	
Yes	20	56	1.46	0.6–3.7	132	247	1.51	1.0–2.2	1.52	1.1–2.2
Pack-years[2]										
1–9	15	35	1.42	0.5–3.9	76	168	1.32	0.9–2.0	1.43	1.0–2.1
10–19	1	12	1.86	0.4–8.5	27	32	2.28	1.2–4.3	1.81	1.0–3.3
≥20	1	1	3.94	0.2–95.0	7	7	2.82[4]	0.9–9.0	2.95[4]	1.0–8.9
ETS exposure in adulthood										
No	19	57	1.00		31	70	1.00		1.00	
Yes	14	57	0.56	0.2–1.4	169	337	1.03	0.6–1.7	0.90	0.6–1.4
Pack-years[2]										
1–9	11	33	0.76	0.3–2.2	52	122	0.81	0.5–1.4	0.81	0.5–1.3
10–19	2	7	0.85	0.1–5.6	48	98	1.00	0.6–1.8	0.90	0.5–1.6
≥20	0	9	—	—	58	102	1.03	0.6–1.8	0.86	0.5–1.5

[1]ORs additionally adjusted for sex.–[2]Pack-years is the sum of cigarettes per day and *liang* per month from pipe smoking divided by 20 times duration of exposure in childhood or adulthood. The summation was based on a empirical evaluation of relative effects.–[3]Test of linear trend, $0.01 < p < 0.05$.–[4]Test of linear trend, $p < 0.01$.

TABLE III – ODDS RATIOS (OR) BY PACK-YEARS OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS) FOR SEVERAL VARIABLES RELATED TO INDOOR DWELLINGS FOR NEVER-SMOKING SUBJECTS (ORS ADJUSTED FOR REFERENCE AGE, PREFECTURE, AND, WHERE APPROPRIATE, EXPOSURE TO ETS IN CHILDHOOD OR ADULTHOOD)

	Cases	Controls	Pack-years of ETS exposure				Pack-years of ETS exposure			
			0	1–9	10–19	≥20	0	1–9	10–19	≥20
			Childhood exposure to ETS				Adulthood exposure to ETS			
Type of current dwelling[1]										
Underground	61	182	1.00	0.76	1.11	1.23	1.00	1.97	2.54	3.10[2]
Standard	137	276	1.00	1.90	2.15	4.99[2]	1.00	0.54	0.59	0.48
Type of longest lived-in dwelling										
Underground	123	252	1.00	1.14	1.21	1.40[3]	1.00	0.72	1.23	1.50[3]
Standard	75	207	1.00	1.74	2.62	10.9[3]	1.00	0.99	0.71	0.38
Time weighted radon concentration (Bq/m^3) for 5–30 years prior to reference age										
<150	14	92	1.00	0.55	2.08	—	1.00	1.89	0.77	1.20
150–249	71	207	1.00	1.37	1.63	3.77[3]	1.00	0.59	0.78	0.76
≥250	40	110	1.00	0.84	1.40	3.86[3]	1.00	0.61	1.17	0.60
Type of fuel used in current dwelling										
Coal	79	106	1.00	1.61	1.44	5.68[4]	1.00	0.73	0.34	0.71
Firewood	43	141	1.00	1.16	0.80	—	1.00	0.88	1.04	1.62[3]
Sticks/twigs	71	207	1.00	1.57	2.56	3.78[2]	1.00	0.92	1.50	0.58
Indoor smoky in winter for current dwelling										
Very/somewhat	29	93	1.00	1.78	2.99	—[4]	1.00	0.53	0.13	0.64
Slightly	64	98	1.00	1.16	2.13	5.23[3]	1.00	0.72	1.87	1.27
Not smoky	104	266	1.00	1.54	1.55	1.62	1.00	0.97	1.01	0.84

[1]Underground dwelling includes all cave-like housing styles. Standard dwelling includes the standard above ground style and apartments.–[2]Test of trend, $p < 0.01$.–[3]Test of trend, $0.01 < p < 0.05$.–[4]Test of trend, $0.05 < p < 0.10$.

(0.9,2.3). Our results were similar to other epidemiologic studies of lung cancer and exposure to ETS, which have consistently shown a 1.2- to 1.5-fold risk of lung cancer (National Research Council, 1986; California Environmental Protection Agency, 1997). Studies of ETS exposure in China are of particular interest, since lung cancer rates in females, who are mostly non-smokers, are high and ORs for lung cancer for active smokers compared with never-smokers have been consistently found to range from 2 to 4 (Liu, 1992). The OR for ever-smokers compared with never-smokers in our complete data was 1.7 (1.2,2.3), and ORs by pack-years of smoking increased monotonically to an OR of 4.5 for 30 and more pack-years of smoking. While ORs for active smokers in our study are low compared with western studies, it nonetheless appears that subjects who are exposed passively to ETS are at a risk comparable to levels found in studies in western countries.

There have been several epidemiologic studies of ETS in China. A meta-analysis of 6 studies reported no overall excess risk for any ETS exposure with OR=0.91, 95% CI (0.8–1.1), although there was a significant trend of increasing risk with increasing exposure, as measured by number of cigarettes per day and years of cohabitation with a smoker (Wang and Zhou, 1997). The interpretation of this meta-analysis however is problematic, since several studies (Gao *et al*., 1987; Lam *et al*., 1987; Geng *et al*., 1988; Liu *et al*., 1993; Wang *et al*., 1994, 1996), which predated the meta-analysis, were not included. Although results from individual studies are mixed, the overall evidence supports an increased risk of lung cancer with ETS exposure (Table IV). Using results in Table IV and a random effects model (Laird and Mosteller, 1990; Whitehead and Whitehead, 1991), a summary OR with 95% CI for exposure to ETS is 1.3 (1.1,1.7). For 0, <20 and ≥20 cigarettes per day of ETS exposure, summary ORs and 95% CIs were 1.0, 1.6 (1.3,2.1), and 2.2 (1.7,3.0), respectively, with $p<0.01$ for the test of trend.

Results from ETS studies to date have not exhibited a consistent pattern for risk from ETS exposures in childhood as compared with

TABLE IV – SUMMARY OF PREVIOUS CASE-CONTROL STUDIES IN CHINA OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS)

Reference	Location	Subjects	Results
Chan and Fung, 1982	Hong Kong	Females: cases, 84; controls, 139	Odds ratio (OR) for ETS exposure at home and work: 0.8 (0.5,1.2)
Lam, 1985	Hong Kong	Females: cases, 60; controls, 144	OR for ETS exposure at home and work: 2.5 (1.5,4.2)
Koo et al., 1987	Hong Kong	Female non-smokers: cases, 86; controls, 136	OR for ETS exposure: 1.6 (0.9,3.1) ORs for husband's cigarettes/d (0, 1–10, 11–20, ≥21: 1.0, 2.3 (0.9,5.9), 1.7 (0.8,3.8), 1.2 (0.5,3.0); *p* for trend 0.16
Gao et al., 1987	Shanghai	Female non-smokers: cases, 246; controls, 375	OR for ETS exposure in: childhood: 1.1 (0.7,1.7); adulthood: 0.9 (0.6,1.4) ORs for years living with smoking husband (<20, 20–29, 30–39, ≥40): 1.0, 1.1 (0.7,1.8), 1.3 (0.8,2.1), 1.7 (1.0,2.9); *p* for trend <0.05[1]
Lam et al., 1987	Hong Kong	Female non-smokers: cases, 199; controls, 335	OR for ETS exposure: 1.7 (1.2,2.2) ORs for husband's cigarettes/d (0, 1–10, 11–20, ≥21): 1.0, 2.2 (1.1,4.2), 1.9 (1.2,2.9), 2.1 (1.1,4.0); *p* for trend <0.01
Geng et al., 1988	Tianjin	Females non-smokers: cases, 54; controls, 93	OR for ETS exposure: OR = 2.16 (1.1,3.8) ORs for husband's cigarettes/d (0, 1–9, 10–19, ≥20): 1.0, 1.4 (1.1,1.8), 2.0 (1.4,2.7), 2.8 (1.9,4.1); *p* for trend <0.05 ORs for years living with smoking spouse (0,1–19,20–39,≥40): 1.0, 1.5 (1.2,1.9), 2.2 (1.5,3.2), 3.3 (2.1,5.2); *p* value for trend <0.05
Wu-Williams et al., 1990	Shenyang and Harbin	Female non-smokers: cases, 417; controls, 602	OR for ETS exposure: 0.8 (0.6,0.9)
Liu et al., 1991	Xuanwei	Female non-smokers: cases, 54; controls, 202	OR for ETS exposure: 0.8 (0.3,1.9)
Liu et al., 1993	Guangzhou	Female non-smokers: cases, 38; controls, 69	ORs for husband's cigarettes/d (0, 1–19, ≥20): 1.0, 0.7 (0.2,2.2), 2.9 (1.2,7.3); *p* for trend = 0.03
Wang et al., 1994	Harbin	Females: 59 pairs smokers; 55 pairs non-smokers	ORs[1] for ETS exposure in: childhood: 3.2 (1.6,6.3); adulthood: 0.85 (0.3,2.3) ORs[1] for household ETS exposure in gm/d (<5, 5-14, ≥15): childhood: 1.0, 2.4 (1.2,4.7), 3.6 (1.5,8.6); *p* for trend <0.01; adulthood: 1.0, 1.0(0.6,1.9), 1.1(0.4,2.9)
Wang et al., 1996	Guangdong	Females: 99 matched pairs	OR for ETS exposure: 2.5 (1.3,5.1)
Du et al., 1996	Guangzhou	Female non-smokers: cases 75, controls, 128	OR for ETS exposure: 1.2 (0.7,2.2) ORs for husbands' cigarettes/d (0, 1–19, ≥20): 1.0, 0.7 (0.3,1.4), 1.6 (0.8,3.2); ORs for years with smoking husband (0, 1–29, ≥30): 1.0, 1.4 (0.6,3.2), 1.2 (0.6,2.3)
Ko et al., 1997	Taiwan	Female non-smokers: 105 matched pairs	ORs for ETS exposed from: parents: 0.8 (0.4,1.6); cohabitants: 1.0 (0.4,2.3); spouses: 1.3 (0.7,2.5)
Zhong et al., 1999	Shanghai	Female non-smokers: cases, 504; controls, 601	ORs for ETS exposure in: childhood: 0.9 (0.7,1.2); adulthood: 1.1 (0.8,1.4); occupation: 1.3 (1.0,1.7)
Current study	Gansu	Non-smokers: Females: cases, 200; controls, 407 Males: cases, 33; 114 controls	OR for ETS exposure: 1.2 (0.7,2.0) ORs for ETS in: childhood: 1.5 (1.1,2.2); adulthood: 0.9 (0.6,1.4); ORs for years occupational ETS (0, <20, ≥20): 1.0, 1.3 (1.0,1.7), 1.8 (0.5,5.6)

[1]*p*-value for trend computed using weighted regression.–[2]ORs for childhood (ages <23) and adulthood (ages ≥23) averaged over categories of age at exposure.

ETS exposures in adulthood. Risk patterns with tobacco use among active smokers are consistent with tobacco smoke being a complete lung carcinogen, serving both as a initiator and promoter (Brown and Chu, 1987; Darby and Pike, 1988; Moolgavkar *et al*., 1989). The identification of ETS exposure as an initiator, particularly with exposures occurring in childhood, would markedly affect estimates of lifetime lung cancer risk from ETS exposure. ORs for ETS exposure in our study varied significantly by period of exposure, with ORs significantly increased with childhood ETS exposure. This result is at odds with the conclusions of Brown and Chu (1987) and Darby and Pike (Darby and Pike, 1988), who fitted the Armitage-Doll multistage model for carcinogenesis to smokers and suggested that a low level of tobacco smoke exposure acts as a late stage carcinogen, with duration of exposure having a relatively lesser effect on risk. However, this conclusion was disputed by Moolgavkar *et al*. (1989) and Whittemore (1988), who suggested that data were too limited for such specific conclusions. Of the three previous China studies that reported results by period of exposure, 1 study found a greater effect of ETS exposure in childhood (Wang *et al*., 1994), while 2 studies found no overall effect of ETS exposure and in particular no difference between ORs for exposures in childhood and adulthood (Gao *et al*., 1987; Zhong *et al*., 1999) (Table IV). Studies in western countries have similarly shown mixed results (see Table 7.6 in California Environmental Protection Agency, 1997; Boffetta *et al*., 1998; Janerich *et al*., 1990). The inconsistency observed to date may be due to the difficulty in recalling details of ETS exposures many years in the past and the relatively small expected effect. Thus, based on published results to date, no definitive conclusions about the relative importance of ETS exposures in childhood and in adulthood are possible.

Owing to the historically higher proportion of smoking males, there is a greater number of males than females diagnosed each year with lung cancer (Boring *et al*., 1994; Travis *et al*., 1996). While evidence is not conclusive, studies of active smokers have suggested that ORs for lung cancer from exposure to tobacco smoke may be at least as great, if not greater, in females than males, after adjusting for smoking duration and rate (Lubin and Blot, 1984; Brownson *et al*., 1992; Risch *et al*., 1993; Zang and Wynder, 1996), suggesting females may have a greater sensitivity to tobacco smoke. Most studies of ETS exposure have been carried out in never-smoking females; however, the few studies of ETS exposure that reported ORs separately for never-smoking females and males found no marked differences of ORs in females and males (Kabat and Wynder, 1984; Kabat *et al*., 1995; Boffetta *et al*., 1998), although investigators did not appear to have conducted formal statistical hypothesis tests. Our study had limited data on males, but the magnitude of the ORs and non-significant tests of homogeneity suggested that females were at comparable risk of lung cancer from ETS exposure.

A strength of our population-based study was its location in a predominantly rural, non-industrial area of China. Fewer than one third of males and one tenth of females were ever employed in non-farm related jobs. In addition, few of those who did worked off the farm reported any exposure to a list of potential lung carcinogens. ORs for ETS exposure were unchanged when data were restricted to subjects who never worked off the farm.

A potential confounding factor in our evaluation of ETS was the level of indoor air pollution, since virtually all subjects burned coal, wood or sticks in a stove or *kang* for cooking and heating. A detailed evaluation of indoor air pollution in 25 houses in the study areas revealed high levels of particle bound polycyclic aromatic hydrocarbons (PAHs), particulate matter smaller than 10 μm (PM-10), CO, NO^2 and SO_2 (Ligman *et al*., 1997). Ventilation rates were high, with an average of 1.5 air changes per hr, resulting in levels of indoor air pollutants that were episodic and followed closely the use of indoor stoves. Pollutant levels were low during non-cooking times. Except for CO and PM-10, mean values for integrated measurements were below U.S. Ambient Air Quality Standards. We did not have measurement data on indoor air pollutants in each house, but in our analysis, OR patterns for ETS exposure were unchanged when adjustment was made for housing type (underground or above-ground dwelling), amount and type of fuel used and the degree of indoor smokiness as reported by the respondent. Values for these potential confounding variables were determined for the current house, the longest lived-in house and for houses in adulthood and in childhood.

We relied on next-of-kin interviews when the case patient was deceased or too ill. Next-of-kin, particularly spouses, may be less knowledgeable about events and exposures occurring in childhood, thus raising the possibility that results may have been affected by differential misclassification of ETS exposure. While non-differential misclassification of an exposure variable most often, although not always, results in ORs closer to the null value (Dosemeci *et al*., 1990), consequences cannot be predicted if misclassification is differential. In our study, ORs were larger for ETS exposure in childhood than in adulthood. These OR patterns could have been influenced by differential misclassification if subjects or next-of-kin of cases were more likely to report ETS exposure than controls. However, this differential recall would had to have differed for exposures in adulthood and in childhood, which seems unlikely. In addition, OR patterns for ETS exposure were similar when data were restricted to subject respondents only.

In summary, we found an overall increasing risk of lung cancer with pack-years of exposure to ETS. This increasing risk with greater ETS exposure was primarily due to exposures occurring in childhood.

ACKNOWLEDGEMENTS

We thank Ms. M. Pacious and Ms. R. Hur, Westat ,Inc., for data management and programming support, and S. Lei, J. Cao, S. Lei and W. Wang of the Laboratory of Industrial Hygiene, Ministry of Public Health, China, for data collection support. We are grateful to members of the expert review panel, Drs. J. Shi, Y. Kang, F. Du, D. Zhao and Y. Wang, for reviewing lung cancer diagnoses.

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